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FACSIMILE COVER LETTER

To:	Examiner Aulakh Central Fax
Firm:	U.S. Patent and Trademark Office
Facsimile:	571 273-0678 571 273-8300
From:	Thomas J. Kowalski
Date:	April 27, 2006
Re:	U.S. Patent Application No. 10/825,758 Steroidal Compounds For Inhibiting Steroid Sulphatase Attorney Docket No. 674519-2030
Number of Pages: (including cover page)	
cc:	

If you do not receive all pages or are unable to read the transmission, please call and ask for Sarah Marcano (Ext. 2064).

Dear Examiner Aulakh:

Attached is a substitute page 96 as you requested in our telephone conference of April 24, 2006.

Please do not hesitate to contact us if you require additional assistance.

Regards,

Sarah A. Marcano
Assistant to Thomas J. Kowalski

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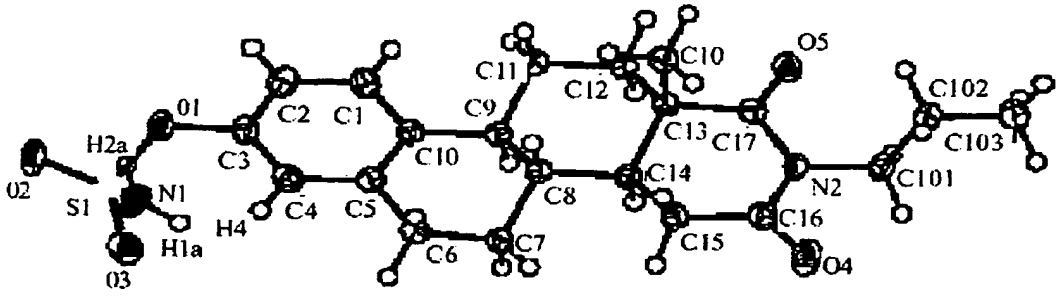
optimum when the alkyl group was an heptyl moiety. Their potency, similar to that of EMATE, clearly underlines the presence of a hydrophobic pocket in the enzyme active site corresponding to the direction of the 17β-substituent.

A weaker inhibition of STS by **41** therefore suggests that the orientation of its side-chain, situated on the N-atom of the D-ring (6-membered), is different enough from that of the 17β-side-chain of **1** or **2** (5-membered D-ring) to induce a decrease of affinity with the active site of the enzyme. It can be proposed that, while there is a hydrophobic pocket in the enzyme active site for 17β-substituents, the topology of the active site around the N-position of a 6-membered ring could be more restrictive to bulky substituents. To corroborate this hypothesis, molecular modelling would be a tool of choice.

In order to elucidate the orientation of the atoms in the D-ring and in the side-chain, as well as gather data for possible future molecular modelling studies, the crystal structure of the highly potent oestrone derivative **39** was determined. A crystal (approx. dimensions 0.20×0.17×0.08 mm), obtained from slow recrystallization in acetone/hexane, was used for data collection.

The ORTEP plot of the asymmetric unit of **41** is shown below along with the labelling scheme used. The sulfamate group, all four rings, and the key features of the modified D-ring are clearly visible. As expected, the D-ring is in a half chair conformation since the imide function implies the position of the atoms C13, C17, N and C1' as well as C15, C16, N and C1' in the same plan.



ORTEP plot of the X-ray crystal structure of **41**. Ellipsoids are shown at the xx% probability level.